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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **RAAV COMPOSITIONS AND METHODS FOR DELIVERY OF HUMAN FACTOR VII POLYPEPTIDES AND TREATMENT OF HEMOPHILIA A**

(57) Abstract: Disclosed are improved recombinant adeno-associated viral (rAAV) vector compositions useful in the delivery of antihemophilic factor polypeptides to selected mammalian host cells. The disclosed rAAV vector compositions preferably comprise one or more polynucleotide sequences that express one or more mammalian Factor VII proteins, polypeptides, peptides, a operably linked to one or more promoter and/or enhancer sequences that are capable of expressing the encoded antihemophilic therapeutics in cells suitably transformed with the disclosed rAAV vector constructs, virions, and viral particles comprising the constructs of interest. These compositions, and methods for their use, including the manufacture of medicaments, have desirable therapeutic and/or prophylactic efficacy in the amelioration, treatment, and/or prevention of a variety of diseases, disorders, and dysfunctions in selected mammals, and in particular, humans diagnosed with Factor VII deficiency and/or hemophilia A.



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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/20746

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A01N 63/00; A61K 48/00

US CL : 424/93.2

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MARGARITIS et al. Long-term expression of activated FVII in vivo following AAV-mediated liver gene transfer: Implications for treatment with continuous infusion of recombinant activated FVII. Blood. November 2001, Vol 98. No. 11 Part 1, page 696a, abstract 2908.	1, 2, 18, 26, 36-42, 45-50
X	US 6,132,729 A (THORPE et al) 17 October 2000 (17.10.2000), see whole document, especially columns 7-10 and 33.	1-17, 26-36, 38-40, 45-50
Y,E	US 2003/0228282 A1 (GAO et al) 11 December 2003 (11.12.2003), see whole document, especially pages 5-12.	1-50
Y,E	US 2003/0013189 A1 (WILSON et al) 16 January 2003 (16.01.2003) see whole document, especially pages 4-6.	24, 25



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T"
"A" document defining the general state of the art which is not considered to be of particular relevance	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"B" earlier application or patent published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

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The special technical feature of group II is considered to be SEQ ID NO: 8.
The special technical feature of group III is considered to be SEQ ID NO: 10.
The special technical feature of group IV is considered to be SEQ ID NO: 12.
The special technical feature of group V is considered to be SEQ ID NO: 14.
The special technical feature of group VI is considered to be SEQ ID NO: 15.
The special technical feature of group VII is considered to be SEQ ID NO: 17.

Accordingly, Group I-VII are not so linked by the same or a corresponding technical feature as to form a single general inventive concept.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: I) each variant has a different mode of action; and II) each variant has a different mode of action.

Continuation of B. FIELDS SEARCHED Item 3:

WEST, STN

search terms: AAV, Factor VII, FVII, hemophilia, adeno associated virus

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 51-64
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-50 (SEQ ID NO: 1 and 2)

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☒

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/US03/20746

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-50, drawn to a recombinant adeno-associated viral (AAV) vector comprising a nucleic acid set forth in SEQ ID NO: 1 or a nucleic acid encoding a human Factor VII peptide set forth in SEQ ID NO: 2.

Group II, claim(s) 1-9, 11-16, 18-30, and 36-50, drawn to a recombinant adeno-associated viral vector comprising a nucleic acid set forth in SEQ ID NO: 7 or a nucleic acid encoding a rat Factor VII peptide set forth in SEQ ID NO: 8.

Group III, claim(s) 1-9, 11-16, 18-30, and 36-50, drawn to a recombinant adeno-associated viral vector comprising a nucleic acid set forth in SEQ ID NO: 9 or a nucleic acid encoding a danio Factor VII peptide set forth in SEQ ID NO: 10.

Group IV, claim(s) 1-9, 11-16, 18-30, and 36-50, drawn to a recombinant adeno-associated viral vector comprising a nucleic acid set forth in SEQ ID NO: 11 or a nucleic acid encoding a murine Factor VII peptide set forth in SEQ ID NO: 12.

Group V, claim(s) 1-9, 11-16, 18-30, and 36-50, drawn to a recombinant adeno-associated viral vector comprising a nucleic acid set forth in SEQ ID NO: 13 or a nucleic acid encoding a chicken Factor VII peptide set forth in SEQ ID NO: 14.

Group VI, claim(s) 1-9, 11-16, 18-30, and 36-50, drawn to a recombinant adeno-associated viral vector comprising a nucleic acid encoding a rabbit Factor VII peptide set forth in SEQ ID NO: 15.

Group VII, claim(s) 1-9, 11-16, 18-30, and 36-50, drawn to a recombinant adeno-associated viral vector comprising a nucleic acid encoding a bovine Factor VII peptide set forth in SEQ ID NO: 17.

In order for more than one species to be examined, the appropriate additional examination fees must be paid. The species are as follows:

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

Group I:

- I) SEQ ID NO: 3 and 4; and
- II) SEQ ID NO: 5 and 6.

The claims are deemed to correspond to the species listed above in the following manner:

- I) claims 3-8, 11-16, 27-30; and
- II) claims 3-8, 11-16, 27-30.

The following claim(s) are generic: claims 1, 2, 9, 18-26, and 36-50.

The inventions listed as Groups I-VII do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The technical feature linking Groups I-VII appears to be that they all relate to an AAV vector comprising a nucleic acid encoding a Factor VII peptide.

However US 5,789,390 (4-8-98) teaches an AAV vector comprising a nucleic acid encoding Factor VII peptide. Therefore, the technical feature linking the inventions of Groups I-VII does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art.

The special technical feature of group I is considered to be SEQ ID NO: 2.